CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-061/SE2-007

21-062/SE2-008

APPROVED LABELING

[redacted]

Rx only

SCHERING CORPORATION

TEQUIN® (gatifloxacin) Tablets
TEQUIN® (gatifloxacin) Injection

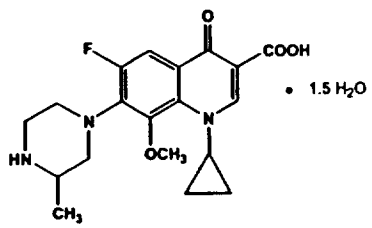
(Patient Information Included)

TEQUIN® is available as TEQUIN (gatifloxacin) Tablets for oral administration and as TEQUIN (gatifloxacin) Injection for intravenous administration.

DESCRIPTION

TEQUIN contains gatifloxacin, a synthetic broad-spectrum 8-methoxyfluoroquinolone antibacterial agent for oral or intravenous administration. Chemically, gatifloxacin is (±) -1-cyclopropyl-6-fluoro-1, 4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

The chemical structure is:



Its empirical formula is $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$ and its molecular weight is 402.42. Gatifloxacin is a sesquihydrate crystalline powder and is white to pale yellow in color. It exists as a racemate, with no net optical rotation. The solubility of the compound is pH dependent. The maximum aqueous solubility (40-60 mg/mL) occurs at a pH range of 2 to 5.

TEQUIN Tablets

TEQUIN Tablets are available as 200-mg and 400-mg white, film-coated tablets and contain the following inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, simethicone, sodium starch glycolate, sorbic acid, and titanium dioxide.

TEQUIN Injection

TEQUIN Injection is available in 20-mL (200-mg) and 40-mL (400-mg) single-use vials as a sterile, preservative-free aqueous solution of gatifloxacin with pH ranging from 3.5 to 5.5. TEQUIN Injection is also available in ready-to-use 100-mL (200-mg) and 200-mL (400-mg) flexible bags as a sterile, preservative-free aqueous solution of gatifloxacin with pH ranging from 3.5 to 5.5. The appearance of the intravenous solution may range

from light yellow to greenish-yellow in color. The color does not affect nor is it indicative of product stability.

The intravenous formulation contains dextrose, anhydrous, USP or dextrose, monohydrate, USP and Water for Injection, USP, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

CLINICAL PHARMACOLOGY

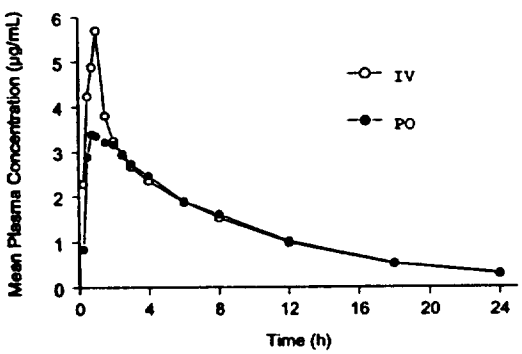
Gatifloxacin is administered as a racemate, with the disposition and antibacterial activity of the R- and S-enantiomers virtually identical.

Absorption

Gatifloxacin is well absorbed from the gastrointestinal tract after oral administration and can be given without regard to food. The absolute bioavailability of gatifloxacin is 96%. Peak plasma concentrations of gatifloxacin usually occur 1-2 hours after oral dosing.

The oral and intravenous routes of administration for TEQUIN can be considered interchangeable, since the pharmacokinetics of gatifloxacin after 1-hour intravenous administration are similar to those observed for orally administered gatifloxacin when equal doses are administered (Figure 1) (see **DOSAGE AND ADMINISTRATION**).

Figure 1. Mean Plasma Concentration-Time Profiles of Gatifloxacin Following Intravenous (IV) and Oral (PO) Administration of a Single 400-mg Dose to Healthy Subjects.



Pharmacokinetics

The mean (SD) pharmacokinetic parameters of gatifloxacin following oral administration to healthy subjects with bacterial infections and subjects with renal insufficiency are listed in Table 1. The mean (SD) pharmacokinetic parameters of gatifloxacin following intravenous administration to healthy subjects are listed in Table 2.

Table 1
Gatifloxacin Pharmacokinetic Parameters– Oral Administration

	C_{max} (µg/mL)	T_{max}[a] (h)	AUC[b] (µg•h /mL)	$T_{½}$ (h)	Cl/F (mL/min)	Cl_R (mL/min)	UR (%)
200 mg – Healthy Volunteers							
Single dose (n=12)	2.0 ± 0.4	1.00 (0.50, 2.50)	14.2 ± 0.4	-	241 ± 40	-	73.8 ± 10.9
400 mg – Healthy Volunteers							
Single dose (n=202)[c]	3.8 ± 1.0	1.00 (0.50, 6.00)	33.0 ± 6.2	7.8 ± 1.3	210 ± 44	151 ± 46	72.4 ± 18.1
Multiple dose (n=18)	4.2 ± 1.3	1.50 (0.50, 4.00)	34.4 ± 5.7	7.1 ± 0.6	199 ± 31	159 ± 34	80.2 ±12.1
400 mg – Patients with Infection							
Multiple dose (n=140)[d]	4.2 ± 1.9	-	51.3 ± 20.4	-	147 ± 48	-	-
400 mg – Single Dose Subjects with Renal Insufficiency							
Cl_{cr} 50 - 89 mL/min (n=8)	4.4 ± 1.1	1.13 (0.75-2.00)	48.0 ± 12.7	11.2 ± 2.8	148 ± 41	124 ± 38	83.7 ± 7.8
Cl_{cr} 30 – 49 mL/min (n=8)	5.1 ± 1.8	0.75 (0.50, 6.00)	74.9 ± 12.6	17.2 ± 8.5	92 ± 17	67 ± 24	71.1 ± 17.4
Cl_{cr} <30 mL/min (n=8)	4.5 ± 1.2	1.50 (0.50, 6.00)	149.3 ± 35.6	30.7 ± 8.4	48 ± 16	23 ± 13	44.7 ± 13.0
Hemodialysis (n=8)	4.7 ± 1.0	1.50 (1.00, 3.00)	180.3 ± 34.4	35.7 ± 7.0	38 ± 8	-	-
CAPD (n=8)	4.7 ± 1.3	1.75 (0.50, 3.00)	227.0 ± 60.0	40.3 ± 8.3	31 ± 8	-	-

[a] Median (Minimum, Maximum)
[b] Single dose: AUC(0–∞), Multiple dose: AUC(0-24)
[c] n=184 for Cl/F, n=134 for Cl_R, and n=132 for UR;
[d] Based on the patient population pharmacokinetic modeling, n=103 for C_{max}
C_{max}: Maximum serum concentration; T_{max}: Time to C_{max}; AUC: Area under concentration versus time curve; $T_{1/2}$: Serum half-life; Cl/F: Apparent total clearance; Cl_R: Renal clearance; UR: Urinary recovery.

Table 2
Gatifloxacin Pharmacokinetic Parameters– Intravenous Administration

	C_{max} (µg/mL)	T_{max}[a] (h)	AUC[b] (µg•h/mL)	$T_{½}$ (h)	Vd_{ss} (L/kg)	Cl (mL/min)	Cl_R (mL/min)	UR (%)
200 mg – Healthy Volunteers								
Single dose (n=12)	2.2 ± 0.3	1.00 (0.67, 1.50)	15.9 ± 2.6	11.1 ± 4.1	1.9 ± 0.1	214 ± 36	155 ± 32	71.7 ± 6.8
Multiple dose (n=8)[c]	2.4 ± 0.4	1.00 (0.67, 1.00)	16.8 ± 3.6	12.3 ± 4.6	2.0 ± 0.3	207 ± 44	155 ± 55	72.4 ± 16.4
400 mg – Healthy Volunteers								
Single dose (n=30)	5.5 ± 1.0	1.00 (0.50, 1.00)	35.1 ± 6.7	7.4 ± 1.6	1.5 ± 0.2	196 ± 33	124 ± 41	62.3 ± 16.7
Multiple dose (n=5)	4.6 ± 0.6	1.00 (1.00, 1.00)	35.4 ± 4.6	13.9 ± 3.9	1.6 ± 0.5	190 ± 24	161± 43	83.5 ± 13.8

[a] Median (Minimum, Maximum)
[b] Single dose: AUC(0–∞), Multiple dose: AUC(0-24)
[c] n=7 for Cl_R and UR
C_{max}: Maximum serum concentration; T_{max}: Time to C_{max}; AUC: Area under concentration versus time curve; $T_{1/2}$: Serum half-life; Vd_{ss}: Volume of distribution; Cl: Total clearance; Cl_R: Renal clearance; UR: Urinary recovery.

Gatifloxacin pharmacokinetics are linear and time-independent at doses ranging from 200 to 800 mg administered over a period of up to 14 days. Steady-state concentrations are achieved by the third daily oral or intravenous dose of gatifloxacin. The mean steady-state peak and trough plasma concentrations attained following a dosing regimen of 400 mg once daily are approximately 4.2 µg/mL and 0.4 µg/mL, respectively, for oral administration and 4.6 µg/mL and 0.4 µg/mL, respectively, for intravenous administration.

Distribution

Serum protein binding of gatifloxacin is approximately 20% in volunteers and is concentration independent. Consistent with the low protein binding, concentrations of gatifloxacin in saliva were approximately equal to those in plasma (mean [range] saliva: plasma ratio was 0.88 [0.46-1.57]). The mean volume of distribution of gatifloxacin at steady-state (Vd_{SS}) ranged from 1.5 to 2.0 L/kg. Gatifloxacin is widely distributed throughout the body into many body tissues and fluids. Rapid distribution of gatifloxacin into tissues results in higher gatifloxacin concentrations in most target tissues than in serum (Table 3).

Table 3
Gatifloxacin Tissue-Fluid/Serum Ratio (Range)[a]

Fluid or Tissue	Tissue-Fluid/Serum Ratio (Range)[a]
Respiratory	
Alveolar macrophages	26.5 (10.9-61.1)
Bronchial mucosa	1.65 (1.12-2.22)
Lung epithelial lining fluid	1.67 (0.81-4.46)
Lung parenchyma	4.09 (0.50-9.22)
Sinus mucosa	1.78 (1.17-2.49)
Sputum (Multiple dose)	1.28 (0.49-2.38)
Reproductive	
Ejaculate	1.07 (0.86-1.32)
Seminal fluid	1.01 (0.81-1.21)
Vagina	1.22 (0.57-1.63)
Cervix	1.45 (0.56-2.64)

[a]Mean of individual ratios collected over 24 hours following single (100, 150, 200, 300, or 400mg) or multiple (150 or 200mg BID) doses of gatifloxacin.

Metabolism

Gatifloxacin undergoes limited biotransformation in humans with less than 1% of the dose excreted in the urine as ethylenediamine and methylethylenediamine metabolites.

In vitro studies with cytochrome P450 isoenzymes (CYP) indicate that gatifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that gatifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes (e.g., midazolam, cyclosporine, warfarin, theophylline).

In vivo studies in animals and humans indicate that gatifloxacin is not an enzyme inducer; therefore, gatifloxacin is unlikely to alter the metabolic elimination of itself or other co-administered drugs.

Excretion

Gatifloxacin is excreted as unchanged drug primarily by the kidney. More than 70% of an administered TEQUIN dose was recovered as unchanged drug in the urine within 48 hours following oral and intravenous administration, and 5% was recovered in the feces. Less than 1% of the dose is recovered in the urine as two metabolites. Crystals of gatifloxacin have not been observed in the urine of normal, healthy human subjects following administration of intravenous or oral doses up to 800 mg.

The mean elimination half-life of gatifloxacin ranges from 7 to 14 hours and is independent of dose and route of administration. Renal clearance is independent of dose with mean value ranging from 124 to 161 mL/min. The magnitude of this value, coupled with the significant decrease in the elimination of gatifloxacin seen with concomitant probenecid administration, indicates that gatifloxacin undergoes both glomerular filtration and tubular secretion. Gatifloxacin may also undergo minimal biliary and/or intestinal elimination, since 5% of dose was recovered in the feces as unchanged drug. This finding is supported by the 5-fold higher concentration of gatifloxacin in the bile compared to the plasma (mean bile: plasma ratio [range] 5.34 [0.33-14.0]).

Special Populations

Patients with Bacterial Infections

The pharmacokinetics of gatifloxacin were similar between healthy volunteers and patients with infection, when underlying renal function was taken into account (see Table 1).

Geriatric

Following a single oral 400-mg dose of gatifloxacin in young (18-40 years) and elderly (≥ 65 years) male and female subjects, there were only modest differences in the pharmacokinetics of gatifloxacin noted in female subjects; elderly females had a 21% increase in C_{max} and a 32% increase in $AUC_{(0-\infty)}$ compared to young females. These differences were mainly due to decreasing renal function with increasing age and are not thought to be clinically important. No dosage adjustment based on age alone is necessary for elderly subjects when administering TEQUIN.

Pediatric

The pharmacokinetics of gatifloxacin in pediatric populations (<18 years of age) have not been established.

Gender

Following a single oral 400-mg dose of gatifloxacin in male and female subjects, there were only modest differences in the pharmacokinetics of gatifloxacin, mainly confined to elderly subjects. Elderly females had a 21% increase in C_{max} and a 33% increase in $AUC_{(0-\infty)}$ compared to elderly males. Both results were accounted for by gender-related differences in body weight and are not thought to be clinically important. Dosage adjustment of TEQUIN(gatifloxacin) is not necessary based on gender.

Chronic Hepatic Disease

Following a single oral 400-mg dose of gatifloxacin in healthy subjects and in subjects with moderate hepatic impairment (Child–Pugh B classification of cirrhosis), C_{max} and $AUC_{(0-\infty)}$ values for gatifloxacin were modestly higher (32% and 23% respectively). Due to the concentration-dependent antimicrobial activity associated with quinolones, the modestly higher C_{max} values in the subjects with moderate hepatic impairment are not expected to negatively impact the outcome of TEQUIN therapy in this population. Dosage adjustment of TEQUIN is not necessary in patients with moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of TEQUIN(gatifloxacin) is unknown.

Renal Insufficiency

Following administration of a single oral 400-mg dose of gatifloxacin to subjects with varying degrees of renal impairment, apparent total clearance of gatifloxacin (Cl/F) was

reduced and systemic exposure (AUC) was increased commensurate with the decrease in renal function (see Table 1). Total gatifloxacin clearance was reduced 57% in moderate renal insufficiency (Cl_{cr} 30-49 mL/min) and 77% in severe renal insufficiency (Cl_{cr} <30 mL/min). Systemic exposure to gatifloxacin was approximately 2 times higher in moderate renal insufficiency and approximately 4 times higher in severe renal insufficiency, compared to subjects with normal renal function. Mean C_{max} values were modestly increased. A reduced dosage of TEQUIN is recommended in patients with creatinine clearance <40 mL/min, including patients requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION: Impaired Renal Function.**)

Diabetes Mellitus

The pharmacokinetics of gatifloxacin in patients with type 2 diabetes (non–insulin-dependent diabetes mellitus), following TEQUIN 400 mg orally for 10 days, were comparable to those in healthy subjects.

Glucose Homeostasis

As with other quinolones, clinical experience has shown that disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported in patients treated concomitantly with TEQUIN and oral hypoglycemic agents with or without insulin. Therefore, careful monitoring of blood glucose is recommended when TEQUIN is administered to diabetic patients receiving treatment with oral hypoglycemic agents with or without insulin. (See **PRECAUTIONS: General, Information for Patients,** and **Drug Interactions**.)

No clinically significant changes in glucose tolerance (via measurement of oral glucose challenge) and glucose homeostasis (via measurement of fasting serum glucose, serum insulin and c-peptide) were observed following single or multiple intravenous infusion doses of 200 to 800 mg TEQUIN in healthy volunteers, or 400-mg oral doses of TEQUIN for 10 days in patients with type 2 diabetes (non–insulin-dependent diabetes mellitus). Transient modest increases in serum insulin and decreases in glucose concentrations were noted with the first dose of intravenous or oral gatifloxacin. Following multiple oral doses of TEQUIN in patients with type 2 non–insulin-dependent diabetes mellitus controlled with glyburide, decreases in serum insulin concentrations were noted following oral glucose challenge; however, these decreases were not accompanied by changes in serum glucose levels. (See **PRECAUTIONS: General**.)

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 48 healthy, male Caucasian volunteers (12 per group), the minimum erythematous dose was measured for ciprofloxacin (500 mg BID), lomefloxacin (400 mg QD), gatifloxacin (400 mg QD), and placebo before and after drug administration for 7 days. In this study, gatifloxacin was comparable to placebo at all wavelengths tested and had a lower potential for producing delayed photosensitivity skin reactions than ciprofloxacin or lomefloxacin.

Electrocardiogram

In volunteer studies assessing oral and IV doses ranging from 200 to 800 mg, 55 subjects had 76 paired valid ECGs. There were no subjects with abnormal QTc intervals (>450 msec); the mean ± SD change in QTc interval was 2.9 ± 16.5 msec.

There is limited information available on the potential for a pharmacodynamic interaction in humans between gatifloxacin and drugs that prolong the QTc interval of an electrocardiogram. Therefore, gatifloxacin should not be used with Class IA and Class III antiarrhythmics. (See **WARNINGS** and **PRECAUTIONS**.)

Spirometry

No clinically significant changes in spirometry were observed following single or multiple 200-mg, 400-mg, 600-mg, and 800-mg intravenous infusion doses of TEQUIN in healthy volunteers.

Drug-Drug Interactions

Systemic exposure to TEQUIN is increased following concomitant administration of TEQUIN and probenecid, and is reduced by concomitant administration of TEQUIN and ferrous sulfate or antacids containing aluminum or magnesium salts. TEQUIN can be administered 4 hours before the administration of dietary supplements containing zinc, magnesium, or iron (such as multivitamins).

Probenecid: Concomitant administration of TEQUIN (single oral 200-mg dose) with probenecid (500 mg BID x 1 day) resulted in a 42% increase in AUC and a 44% longer half-life of gatifloxacin.

Iron: When TEQUIN (single oral 400-mg dose) was administered concomitantly with ferrous sulfate (single oral 325-mg dose), bioavailability of gatifloxacin was reduced (54% reduction in mean C_{max} and 35% reduction in mean AUC). Administration of TEQUIN (single oral 400-mg dose) 2 hours after or 2 hours before ferrous sulfate (single oral 325-mg dose) did not significantly alter the oral bioavailability of gatifloxacin. (See **DOSAGE AND ADMINISTRATION**.)

Antacids: When TEQUIN (single oral 400-mg dose) was administered 2 hours before, concomitantly, or 2 hours after an aluminum/magnesium-containing antacid (1800 mg of aluminum oxide and 1200 mg of magnesium hydroxide single oral dose), there was a 15%, 69%, and 47% reduction in C_{max} and a 17%, 64%, and 40% reduction in AUC of gatifloxacin, respectively. An aluminum/magnesium-containing antacid did not have a clinically significant effect on the pharmacokinetics of gatifloxacin when administered 4 hours after gatifloxacin administration (single oral 400-mg dose). (See **DOSAGE AND ADMINISTRATION**.)

Milk, Calcium, and Calcium-containing Antacids: No significant pharmacokinetic interactions occur when milk or calcium carbonate is administered concomitantly with TEQUIN. Concomitant administration of 200 mL of milk or 1000 mg of calcium carbonate with TEQUIN (200-mg gatifloxacin dose for the milk study and 400-mg gatifloxacin dose for the calcium carbonate study) had no significant effect on the pharmacokinetics of gatifloxacin. TEQUIN can be administered 4 hours before the administration of dietary supplements containing zinc, magnesium, or iron (such as multivitamins).

Minor pharmacokinetic interactions occur following concomitant administration of gatifloxacin and digoxin; a priori dosage adjustments of either drug are not warranted.

Digoxin: Overall, only modest increases in C_{max} and AUC of digoxin were noted (12% and 19% respectively) in 8 of 11 healthy volunteers who received concomitant administration of TEQUIN (400-mg oral tablet, once daily for 7 days) and digoxin (0.25 mg orally, once daily for 7 days). In 3 of 11 subjects, however, a significant increase in digoxin concentrations was observed. In these 3 subjects, digoxin C_{max} increased by 18%, 29%, and 58% while digoxin AUC increased by 66%, 104%, and 79%, and digoxin clearance decreased by 40%, 51%, and 45%. Although dose adjustments for digoxin are not warranted with initiation of gatifloxacin treatment, patients taking digoxin should be monitored for signs and/or symptoms of toxicity. In patients who display signs and/or symptoms of digoxin intoxication, serum digoxin concentrations should be determined, and digoxin dosage should be adjusted as appropriate. The pharmacokinetics of gatifloxacin was not altered by digoxin.

No significant pharmacokinetic interactions occur when cimetidine, midazolam, theophylline, warfarin, or glyburide is administered concomitantly with TEQUIN. These results and the data from *in vitro* studies suggest that gatifloxacin is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2D6 isoenzymes.

Cimetidine: Administration of TEQUIN (single oral dose of 200 mg) 1 hour after cimetidine (single oral dose of 200 mg) had no significant effect on the pharmacokinetics of gatifloxacin. These results suggest that absorption of gatifloxacin is expected to be unaffected by H_2-receptor antagonists like cimetidine.

Midazolam: TEQUIN administration had no significant effect on the systemic clearance of intravenous midazolam. A single intravenous dose of midazolam (0.0145 mg/kg) had no effect on the steady-state pharmacokinetics of gatifloxacin (once daily oral doses of 400 mg for 5 days). These results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP3A4 isoenzyme.

Theophylline: Concomitant administration of TEQUIN (once daily oral doses of 400 mg for 5 days) and theophylline (300 mg BID oral dose for 10 days) had no significant effect on the pharmacokinetics of either drug. These results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP1A2 isoenzyme.

Warfarin: Concomitant administration of TEQUIN (once daily oral doses of 400 mg for 11 days) and warfarin (single oral dose of 25 mg) had no significant effect on the pharmacokinetics of either drug nor was the prothrombin time significantly altered. These results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP2C9, CYP1A2, CYP3A4, and CYP2C19 isoenzymes. (See **PRECAUTIONS: Drug Interactions.**)

Glyburide: Concomitant administration of TEQUIN (once daily oral doses of 400 mg for 10 days) and glyburide (steady-state once daily regimen) in patients with type 2 diabetes mellitus had no significant effects on the disposition of either drug, nor were the fasting glucose levels significantly changed. These results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP3A4 isoenzyme. **(See PRECAUTIONS: General and Drug Interactions.)**

Microbiology

Gatifloxacin is an 8-methoxyfluoroquinolone with *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The antibacterial action of

gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. It appears that the C-8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram-positive bacteria compared to the non-methoxy C-8 moiety.

The mechanism of action of fluoroquinolones including gatifloxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between gatifloxacin and the mentioned classes of antibiotics.

From *in vitro* synergy tests, gatifloxacin, as with other fluoroquinolones, is antagonistic with rifampin against enterococci.

Resistance to gatifloxacin *in vitro* develops slowly via multiple-step mutations. Resistance to gatifloxacin *in vitro* occurs at a general frequency of between 1×10^{-7} to 10^{-10}. Although cross-resistance has been observed between gatifloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gatifloxacin.

Gatifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae (penicillin-susceptible strains)

Aerobic gram-negative microorganisms
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis

Other microorganisms
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**

Gatifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤2 µg/mL (≤1 µg/mL for *Streptococcus pneumoniae*) against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of gatifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms
Staphylococcus saprophyticus

Streptococcus pneumoniae (penicillin-resistant strains)
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Acinetobacter lwoffii
Citrobacter koseri
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris

[redacted]

Anaerobic microorganisms
Peptostreptococcus species

NOTE: The activity of gatifloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum* (see **WARNINGS**).

NOTE: Extended-spectrum β-lactamase producing gram-negative microorganisms may have reduced susceptibility to quinolones.

Susceptibility Tests

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method [1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gatifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae* and *Staphylococcus* species:

MIC (μg/mL)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[a]:

[redacted]

MIC (μg/mL)	Interpretation
≤0.5	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[b]:

MIC (µg/mL)	Interpretation
≤1.0	Susceptible (S)
2.0	Intermediate (I)
≥4.0	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Neisseria gonorrhoeae*[c]:

MIC (µg/mL)	Interpretation
≤0.125	Susceptible (S)
0.25	Intermediate (I)
≥0.5	Resistant (R)

[c] These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gatifloxacin powder should provide the following MIC values:

Microorganism	MIC Range (µg/mL)
Enterococcus faecalis ATCC 29212	0.12 – 1.0
Escherichia coli ATCC 25922	0.008 – 0.03
Haemophilus influenzae ATCC 49247[d]	0.004 – 0.03
Neisseria gonorrhoeae ATCC 49226[e]	0.002 – 0.016
Pseudomonas aeruginosa ATCC 27853	0.5 – 2.0
Staphylococcus aureus ATCC 29213	0.03 – 0.12
Streptococcus pneumoniae ATCC 49619[f]	0.12 – 0.5

[d] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[1]

[e] This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement.[1]

[f] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum

concentrations. This procedure uses paper disks impregnated with 5-µg gatifloxacin to test the susceptibility of microorganisms to gatifloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg gatifloxacin disk should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing *Enterobacteriaceae* and *Staphylococcus* species:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)
15 – 17	Intermediate (I)
≤14	Resistant (R)

For testing *Haemophilus influenzae* and *Hemophilus parainfluenzae*[g]:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)

[g] This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[h]:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)
15 – 17	Intermediate (I)
≤14	Resistant (R)

[h] These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.[2]

For testing *Neisseria gonorrhoeae*[i]:

Zone Diameter (mm)	Interpretation
≥38	Susceptible (S)
34 – 37	Intermediate (I)
≤33	Resistant (R)

[i] These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gatifloxacin.[2]

As with standardized dilution techniques, methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg gatifloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter Range (mm)
Escherichia coli ATCC 25922	30-37
Haemophilus influenzae ATCC 49247[j]	33-41
Neisseria gonorrhoeae ATCC 49226[k]	45-56
Pseudomonas aeruginosa ATCC 27853	20-28
Staphylococcus aureus ATCC 25923	27-33
Streptococcus pneumoniae ATCC 49619[l]	24-31

[j] This quality control range applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using *Haemophilus* Test Medium (HTM)[2].

[k] This quality control range is only applicable to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement[2].

[l] This quality control range is applicable only to tests conducted with *S. pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

INDICATIONS AND USAGE

TEQUIN (gatifloxacin) is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINSTRATION.**)

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis,* or *Staphylococcus aureus.*

Acute sinusitis due to *Streptococcus pneumoniae* or *Haemophilus influenzae.*

Community-acquired pneumonia due to *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Legionella pneumophila.*

Uncomplicated urinary tract infections (cystitis) due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*

Complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*

Pyelonephritis due to *Escherichia coli.*

Uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae.* **Acute, uncomplicated rectal infections in women** due to *Neisseria gonorrhoeae.* (See **WARNINGS.**)

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to gatifloxacin. Therapy with TEQUIN may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

CONTRAINDICATIONS

TEQUIN is contraindicated in persons with a history of hypersensitivity to gatifloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF GATIFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.)

GATIFLOXACIN MAY HAVE THE POTENTIAL TO PROLONG THE QTc INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. DUE TO THE LACK OF CLINICAL EXPERIENCE, GATIFLOXACIN SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QTc INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA, AND PATIENTS RECEIVING CLASS IA (E.G., QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G., AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS.

Pharmacokinetic studies between gatifloxacin and drugs that prolong the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gatifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. In premarketing clinical trials, no cardiovascular morbidity or mortality attributable to QTc prolongation occurred with gatifloxacin treatment in over 4000 patients, including 118 patients concurrently receiving drugs known to prolong the QTc interval and 139 patients with uncorrected hypokalemia (ECG monitoring was not performed).

The likelihood of QTc prolongation may increase with increasing concentrations of the drug; therefore, the recommended dose should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes.

As with other members of the quinolone class, gatifloxacin has caused arthropathy and/or chondrodysplasia in immature dogs. The relevance of these findings to the clinical use of gatifloxacin is unknown. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure, and psychosis have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) stimulation, which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, and insomnia. These reactions may occur following the first dose. If these reactions occur in patients receiving gatifloxacin, the drug should be discontinued and appropriate measures instituted. (See **ADVERSE REACTIONS**.)

As with other quinolones, TEQUIN should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral atherosclerosis, epilepsy, and other factors that predispose to seizures.

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions.

TEQUIN should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment

with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See **PRECAUTIONS**.)

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving antibacterial therapy. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including TEQUIN, and may range in severity from mild to life-threatening. It is important, therefore, to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Although not seen in clinical trials of TEQUIN, ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. TEQUIN should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones.

Gatifloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis.

PRECAUTIONS

General

Quinolones may cause central nervous system (CNS) events including nervousness, agitation, insomnia, anxiety, nightmares, or paranoia. (See **WARNINGS** and **PRECAUTIONS: Information for Patients**.)

Administer gatifloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of gatifloxacin may be reduced. In patients with impaired renal function (creatinine clearance < 40 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of gatifloxacin due to decreased clearance. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION.**)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with TEQUIN, usually in diabetic patients receiving concomitant treatment with oral hypoglycemic agents (e.g., glyburide) with or without insulin. In these patients, the careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with TEQUIN, appropriate therapy should be initiated immediately and TEQUIN should be discontinued. (See **CLINICAL PHARMACOLOGY, PRECAUTIONS: Drug Interactions,** and **ADVERSE REACTIONS.)**

Information for Patients (See **Patient Information** section.)

To assure safe and effective use of TEQUIN, the following information and instructions should be communicated to the patient when appropriate.

Patients should be advised:

- that TEQUIN may produce changes in the electrocardiogram (QTc interval prolongation);
- that TEQUIN should be avoided in patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents;
- that TEQUIN should be used with caution in patients receiving drugs that may effect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants;
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, or recent myocardial ischemia;
- to inform their physician of any other medications when taken concurrently with TEQUIN, including over-the-counter medications;
- to contact their physician if they experience palpitations or fainting spells while taking TEQUIN;
- that TEQUIN Tablets may be taken with or without meals;
- that TEQUIN Tablets should be taken 4 hours before any aluminum- or magnesium-based antacids (see **PRECAUTIONS: Drug Interactions**);
- that TEQUIN Tablets should be taken at least 4 hours before the administration of ferrous sulfate or dietary supplements containing zinc, magnesium, or iron (such as multivitamins) (see **PRECAUTIONS: Drug Interactions**);
- that TEQUIN should be taken 4 hours before VIDEX® (didanosine) buffered tablets, buffered solution, or buffered powder for oral suspension;
- that TEQUIN may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat,

hoarseness), or other symptoms of an allergic reaction (see **WARNINGS** and **ADVERSE REACTIONS**);

- that if they are diabetic, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported in patients treated concomitantly with TEQUIN (as with other quinolones) and oral hypoglycemic agents with or without insulin. If a hypoglycemic reaction occurs, they should initiate appropriate therapy immediately, discontinue TEQUIN, and contact a physician (see **PRECAUTIONS: General** and **Drug Interactions**).
- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon;
- that TEQUIN may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination;
- that phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with TEQUIN at the recommended dose. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds). If sunburn-like reaction or skin eruptions occur, contact their physician. (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential.**)
- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is a history of this condition.

Drug Interactions

TEQUIN (gatifloxacin) can be taken 4 hours before ferrous sulfate, dietary supplements containing zinc, magnesium, or iron (such as multivitamins), or aluminum/magnesium-containing antacids without any significant pharmacokinetic interactions. (See **CLINICAL PHARMACOLOGY**.)

Milk, calcium carbonate, cimetidine, theophylline, warfarin, or midazolam: No significant interactions have been observed when administered concomitantly with TEQUIN. No dosage adjustments are necessary when these drugs are administered concomitantly with TEQUIN. (See **CLINICAL PHARMACOLOGY.**)

Antidiabetic agents: No significant pharmacokinetic interactions have been observed when glyburide was administered concomitantly with TEQUIN. However, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported in patients treated concomitantly with TEQUIN (as with other quinolones) and oral hypoglycemic agents with or without insulin. Therefore, careful monitoring of blood glucose is recommended when TEQUIN is administered to diabetic patients receiving treatment with oral hypoglycemic agents with or without insulin. (See **CLINICAL PHARMACOLOGY** and **PRECAUTIONS: General** and **Information for Patients.**)

Digoxin: Concomitant administration of TEQUIN and digoxin did not produce significant alteration of the pharmacokinetics of gatifloxacin; however, an increase in digoxin concentrations was observed for 3 of 11 subjects. Patients taking digoxin should therefore be monitored for signs and/or symptoms of toxicity. In patients who display signs and/or symptoms of digoxin intoxication, serum digoxin concentrations should be determined, and digoxin dosage should be adjusted as appropriate. (See **CLINICAL PHARMACOLOGY**.)

Probenecid: The systemic exposure of TEQUIN is significantly increased following the concomitant administration of TEQUIN and probenecid. (See **CLINICAL PHARMACOLOGY**.)

Warfarin: In subjects receiving warfarin, no significant change in clotting time was observed when gatifloxacin was coadministered. However, because some quinolones have been reported to enhance the effects of warfarin or its derivatives, prothrombin time or other suitable anticoagulation test should be monitored closely if a quinolone antimicrobial is administered with warfarin or its derivatives.

Nonsteroidal anti-inflammatory drugs (NSAIDS): Although not observed with gatifloxacin in preclinical and clinical trials, the concomitant administration of nonsteroidal anti-inflammatory drugs with a quinolone may increase the risks of CNS stimulation and convulsions (see **WARNINGS**).

Laboratory Test Interactions

There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

B6C3F1 mice given gatifloxacin in the diet for 18 months at doses with an average intake of up to 81 mg/kg/day in males and 90 mg/kg/day in females showed no increases in neoplasms. These doses are approximately 0.13 and 0.18 times the maximum recommended human dose based upon daily systemic exposure (AUC).

In a 2-year dietary carcinogenicity study in Fischer 344 rats, no increases in neoplasms were seen in males given doses up to 47 mg/kg/day and females given up to 139 mg/kg/day. These doses are approximately 0.36 (males) and 0.81 (females) times the maximum recommended human dose based upon daily systemic exposure. A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in males treated with a high dose of 100 mg/kg/day (approximately 0.74 times the maximum recommended human dose based upon daily systemic exposure) versus controls. Although Fischer 344 rats have a high spontaneous background rate of LGL leukemia, the incidence in high-dose males slightly exceeded the historical control range established for this strain. The findings in high-dose males are not considered a concern with regard to the safe use of gatifloxacin in humans.

In genetic toxicity tests, gatifloxacin was not mutagenic in several strains of bacteria used in the Ames test; however, it was mutagenic to *Salmonella* strain TA102. Gatifloxacin was negative in four *in vivo* assays that included oral and intravenous micronucleus tests in mice, an oral cytogenetics test in rats, and an oral DNA repair test in rats. Gatifloxacin was positive in *in vitro* gene-mutation assays in Chinese hamster V-79 cells and *in vitro* cytogenetics assays in Chinese hamster CHL/IU cells. These findings were not unexpected; similar findings have been seen with other quinolones and may be due to the inhibitory effects of high concentrations on eukaryotic type II DNA topoisomerase.

There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately equivalent to the maximum human dose based on systemic exposure [AUC]).

Pregnancy: Category C

There were no teratogenic effects observed in rats or rabbits at oral gatifloxacin doses up to 150 or 50 mg/kg, respectively (approximately 0.7 and 1.9 times the maximum human

dose based on systemic exposure). However, skeletal malformations were observed in fetuses from rats given 200 mg/kg/day orally or 60 mg/kg/day intravenously during organogenesis. Developmental delays in skeletal ossification, including wavy ribs, were observed in fetuses from rats given oral doses of ≥ 150 mg/kg or intravenous doses of ≥30 mg/kg daily during organogenesis, suggesting that gatifloxacin is slightly fetotoxic at these doses. Similar findings have been seen with other quinolones. These changes were not seen in rats or rabbits given oral doses of gatifloxacin up to 50 mg/kg (approximately 0.2 and 1.9 times the maximum human dose, respectively, based on systemic exposure).

When rats were given oral doses of 200 mg/kg of gatifloxacin beginning in late pregnancy and continuing throughout lactation, late postimplantation loss increased, as did neonatal and perinatal mortalities. These observations also suggest fetotoxicity. Similar findings have been seen with other quinolones.

Because there are no adequate and well-controlled studies in pregnant women, TEQUIN should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers

Gatifloxacin is excreted in the breast milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when gatifloxacin is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of gatifloxacin in pediatric populations (< 18 years of age) have not been established. Quinolones, including gatifloxacin, cause arthropathy and osteochondrotoxicity in juvenile animals (rats and dogs).

Geriatric Use

In multiple-dose clinical trials of gatifloxacin (N=2891), 22% of patients were ≥65 years of age and 10% were ≥75 years of age. No overall differences in safety or efficacy were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **DOSAGE AND ADMINISTRATION**.)

ADVERSE REACTIONS

Over 5000 patients have been treated with gatifloxacin in single- and multiple-dose clinical efficacy trials worldwide.

In gatifloxacin studies, the majority of adverse reactions were described as mild in nature. Gatifloxacin was discontinued for adverse events thought related to drug in 2.7% of patients.

Drug-related adverse events classified as possibly, probably, or definitely related with a frequency of ≥3% in patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows: nausea 8%, vaginitis 6%, diarrhea 4%, headache 3%, dizziness 3%.

In patients who were treated with either intravenous gatifloxacin or with intravenous followed by oral therapy, the incidence of adverse events was similar to those who received oral therapy alone. Local injection site reactions (redness at injection site) were noted in 5% of patients.

Additional drug-related adverse events (possibly, probably, or definitely related) considered clinically relevant that occurred in ≥0.1% to <3% of patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows:

Body as a Whole: allergic reaction, asthenia, back pain, chest pain, chills, face edema, fever

Cardiovascular System: hypertension, palpitation

Digestive System: abdominal pain, anorexia, constipation, dyspepsia, flatulence, gastritis, glossitis, mouth ulcer, oral moniliasis, stomatitis, vomiting

Metabolic/Nutritional System: hyperglycemia, peripheral edema, thirst

Musculoskeletal System: arthralgia, leg cramp

Nervous System: abnormal dream, agitation, anxiety, confusion, insomnia, nervousness, paresthesia, somnolence, tremor, vasodilatation, vertigo

Respiratory System: dyspnea, pharyngitis

Skin/Appendages: dry skin, pruritus, rash, sweating

Special Senses: abnormal vision, taste perversion, tinnitus

Urogenital System: dysuria

Additional drug-related adverse events considered clinically relevant that occurred in <0.1% (rare adverse events) of patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows: abnormal thinking, alcohol intolerance, arthritis, asthma (bronchospasm), ataxia, bone pain, bradycardia, breast pain, cheilitis, colitis, convulsion, cyanosis, depersonalization, depression, diabetes mellitus, dysphagia, ear pain, ecchymosis, edema, epistaxis, euphoria, eye pain, eye photosensitivity, gastrointestinal hemorrhage, generalized edema, gingivitis, halitosis, hallucination, hematemesis, hematuria, hostility, hyperesthesia, hypertonia, hyperventilation, hypoglycemia, lymphadenopathy, maculopapular rash, metrorrhagia, migraine, mouth edema, myalgia, myasthenia, neck pain, panic attack, paranoia, parosmia, photophobia, pseudomembranous colitis, psychosis, ptosis, rectal hemorrhage, stress, substernal chest pain, tachycardia, taste loss, tongue edema, vesiculobullous rash.

Laboratory Changes

Clinically relevant changes in laboratory parameters, without regard to drug relationship, occurred in fewer than 1% of TEQUIN-treated patients. These included the following: neutropenia, increased ALT or AST levels, alkaline phosphatase, bilirubin, serum amylase, and electrolytes abnormalities. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

OVERDOSAGE

Gatifloxacin exhibits a low potential for acute toxicity in animal studies. The minimum lethal oral doses in rats and dogs were greater than 2000 mg/kg and 1000 mg/kg, respectively. The minimum lethal intravenous dose was 144 mg/kg in rats and greater

than 45 mg/kg in dogs. Clinical signs observed included decreased activity and respiratory rate, vomiting, tremors, and convulsions.

In the event of acute oral overdose, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed (including ECG monitoring) and given symptomatic and supportive treatment. Adequate hydration should be maintained. Gatifloxacin is not efficiently removed from the body by hemodialysis (approximately 14% recovered over 4 hours) or by chronic ambulatory peritoneal dialysis (CAPD) (approximately 11% recovered over 8 days).

DOSAGE AND ADMINISTRATION

The recommended dosage for TEQUIN Tablets or TEQUIN Injection is described in Table 4. Doses of TEQUIN are administered once every 24 hours. These recommendations apply to all patients with a creatinine clearance ≥ 40 mL/min. For patients with a creatinine clearance <40 mL/min, see the **Impaired Renal Function** subsection.

TEQUIN can be administered without regard to food, including milk and dietary supplements containing calcium.

Oral doses of TEQUIN should be administered at least 4 hours before the administration of ferrous sulfate, dietary supplements containing zinc, magnesium, or iron (such as multivitamins), aluminum/magnesium-containing antacids, or VIDEX® (didanosine) buffered tablets, buffered solution, or buffered powder for oral suspension.

TEQUIN can be administered without regard to age (≥ 18 years) or gender.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with TEQUIN Injection may be switched to TEQUIN Tablets when clinically indicated at the discretion of the physician.

TEQUIN Injection should be administered by INTRAVENOUS infusion only. It is not intended for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Single-use vials require dilution prior to administration. (See *Preparation of Gatifloxacin for Intravenous Administration.*)

TEQUIN Injection should be administered by intravenous infusion over a period of 60 minutes. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION SHOULD BE AVOIDED.

Table 4 Gatifloxacin - Dosage Guidelines		
Infection[a]	**Daily Dose**[b]	**Duration**
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	5 days
Acute Sinusitis	400 mg	10 days
Community-acquired Pneumonia	400 mg	7-14 days
Uncomplicated Urinary Tract Infections (cystitis)	400 mg or 200 mg	Single dose 3 days
Complicated Urinary Tract Infections	400 mg	7-10 days
Acute Pyelonephritis	400 mg	7-10 days
Uncomplicated Urethral Gonorrhea in Men; Endocervical and Rectal Gonorrhea in Women	400 mg	Single dose

[a] due to the designated pathogens (see **INDICATIONS AND USAGE**).
[b] for either the oral or intravenous routes of administration for TEQUIN (see **CLINICAL PHARMACOLOGY**).

Impaired Renal Function

Since gatifloxacin is eliminated primarily by renal excretion, a dosage modification of TEQUIN is recommended for patients with creatinine clearance < 40 mL/min, including patients on hemodialysis and on CAPD. The recommended dosage of TEQUIN (gatifloxacin) is:

Table 5 Recommended Dosage of TEQUIN in Adult Patients with Renal Impairment		
Creatinine Clearance	**Initial Dose**	**Subsequent Dose**[a]
≥ 40 mL/min	400 mg	400 mg every day
<40 mL/min	400 mg	200 mg every day
Hemodialysis	400 mg	200 mg every day
Continuous peritoneal dialysis	400 mg	200 mg every day

[a] Start subsequent dose on Day 2 of dosing.

Administer TEQUIN after a dialysis session for patients on hemodialysis.

Single 400-mg dose TEQUIN regimen (for the treatment of uncomplicated urinary tract infections and gonorrhea) and 200 mg once daily for 3 days TEQUIN regimen (for the treatment of uncomplicated urinary tract infections) require no dosage adjustment in patients with impaired renal function.

The following formula may be used to estimate creatinine clearance:

$$\text{Men: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

Chronic Hepatic Disease

No adjustment in the dosage of TEQUIN is necessary in patients with moderate hepatic impairment (Child-Pugh Class B). There are no data in patients with severe hepatic impairment (Child-Pugh Class C). (See **CLINICAL PHARMACOLOGY**.)

Intravenous Administration

Preparation of Gatifloxacin for Intravenous Administration

TEQUIN solution in single-use vials: TEQUIN Injection is supplied in single-use 20 or 40 mL vials (10 mg/mL) containing a concentrated solution of gatifloxacin in 5% dextrose (200 or 400 mg of gatifloxacin, respectively). (See **HOW SUPPLIED.**) THESE TEQUIN INJECTION SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION. The concentration of the resulting diluted solution should be 2 mg/mL prior to administration.

Compatible intravenous solutions: Any of the following intravenous solutions may be used to prepare a 2 mg/mL gatifloxacin solution:

5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP
5% Sodium Bicarbonate Injection, USP
Plasma-Lyte® 56 and 5% Dextrose Injection (Multiple Electrolytes and Dextrose Injection, Type 1, USP)
M/6 Sodium Lactate Injection, USP
Water for Injection, USP

Gatifloxacin solutions at 2 mg/mL also have been shown to be compatible with 20 mEq/L Potassium Chloride in 5% Dextrose and 0.45% Sodium Chloride Injection, USP.

This intravenous drug product should be inspected visually for particulate matter prior to dilution and administration. Samples containing visible particles should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final intravenous solution. Since the vials are for single-use only, any unused portion remaining in the vial should be discarded.

Since only limited data are available on the compatibility of gatifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to TEQUIN Injection in single-use vials or infused simultaneously through the same intravenous line.

If the same intravenous line is used for sequential infusion of different drugs, the line should be flushed before and after infusion of TEQUIN Injection with an infusion solution compatible with TEQUIN Injection and with any other drug(s) administered via this common line.

If TEQUIN Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

TEQUIN Injection premix in single-use flexible containers: TEQUIN Injection is also available in ready-to-use 100- and 200-mL flexible bags containing a dilute solution of 200 or 400 mg gatifloxacin in 5% dextrose. NO FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.

This intravenous drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Plasma-Lyte® is a registered trademark of Baxter International Inc.

Since the premix flexible bags are for single use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of gatifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to TEQUIN Injection in flexible containers or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of different drugs, the line should be flushed before and after infusion of TEQUIN Injection with an infusion solution compatible with TEQUIN Injection and with any other drug(s) administered via this common line.

Instructions for the use of TEQUIN Injection premix in flexible containers:

To open:

1. Tear outer wrap at the notch and remove solution container.
2. Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.
3. Use only if solution is clear and light yellow to greenish-yellow in color.
4. Use sterile equipment.
5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration:

1. Close flow control clamp of administration set.
2. Remove cover from port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated.
   NOTE: See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of TEQUIN Injection premix in flexible containers.
6. Open flow control clamp to expel air from set. Close clamp.
7. Regulate rate of administration with flow control clamp.

Stability of TEQUIN Injection as Supplied

When stored under recommended conditions, TEQUIN Injection, as supplied in 20-mL and 40-mL vials and in 100-mL and 200-mL flexible containers, is stable through the expiration date printed on the label.

Stability of TEQUIN Injection Following Dilution

TEQUIN Injection, when diluted in a compatible intravenous fluid to a concentration of 2 mg/mL, is stable for 14 days when stored between 20° C to 25° C or when stored under refrigeration between 2° C to 8° C.

TEQUIN Injection, when diluted to a concentration of 2 mg/mL in a compatible intravenous fluid EXCEPT FOR 5% SODIUM BICARBONATE INJECTION, USP, may be stored for up to 6 months at –25° C to –10° C (–13° F to 14° F). Frozen solutions may be thawed at controlled room temperature. Solutions that have been thawed are

stable for 14 days after removal from the freezer when stored between 20° C to 25° C or when stored under refrigeration between 2° C to 8° C. Solutions should not be refrozen.

HOW SUPPLIED

Tablets

TEQUIN® (gatifloxacin) Tablets are available as 200-mg and 400-mg white, film-coated tablets. The tablets are almond shaped and biconvex and contain gatifloxacin sesquihydrate equivalent to either 200 mg or 400 mg gatifloxacin.

TEQUIN Tablets are packaged in bottles, unit dose blister strips, and blister packs of 7 tablets (TEQUIN Teq-Paq™) in the following configurations:

200 mg tablets—color: white; shape: biconvex; debossing: "BMS" on one side and "TEQUIN" and "200" on the other.

Bottles of 30 (NDC 0015-1117-50)
Blister pack of 100 (NDC 0015-1117-80)

400 mg tablets—color: white; shape: biconvex; debossing: "BMS" on one side and "TEQUIN" and "400" on the other.

Bottles of 50 (NDC 0015-1177-60)
Blister pack of 100 (NDC 0015-1177-80)
Carton of 2 TEQUIN Teq-Paqs (7 tablets each) (NDC 0015-1177-19)

Storage

Store at 25° C (77° F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature].

Intravenous Solution – Single-use Vials

TEQUIN® (gatifloxacin) Injection is available for intravenous administration in the following configurations:

Single-use vials containing a clear, light yellow to greenish-yellow solution at a concentration of 10 mg/mL gatifloxacin.

10 mg/mL (200 mg), 20-mL vials (NDC 0015-1178-80)
10 mg/mL (400 mg), 40-mL vials (NDC 0015-1179-80)

Storage

Store at 25° C (77°F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature].

Intravenous Solution – Premix Bags

TEQUIN Injection is also available in ready-to-use flexible bags containing a dilute solution of 200 mg or 400 mg of gatifloxacin in 5% dextrose. Premix bags are manufactured by Abbott Laboratories in North Chicago, IL.

2 mg/mL (200 mg), 100-mL flexible container (NDC 0015-1180-80)
2 mg/mL (400 mg), 200-mL flexible container (NDC 0015-1181-80)

Storage

Store at 25° C (77° F); excursions permitted to 15° to 30° C (59° to 86° F) [see USP Controlled Room Temperature]. Do not freeze.

ANIMAL PHARMACOLOGY

In contrast to some other quinolone antibacterials, there was no evidence of phototoxicity when gatifloxacin was evaluated in the hairless mouse or guinea pig models using simulated sunlight or UVA radiation, respectively.

Unlike some other members of the quinolone class, crystalluria, ocular toxicity, and testicular degeneration were not observed in 6-month repeat dose studies with rats or dogs given gatifloxacin.

While some quinolone antibacterials have proconvulsant activity that is exacerbated with concomitant use of nonsteroidal antiinflammatory drugs (NSAID), gatifloxacin did not produce an increase in seizure activity when administered intravenously to mice at doses up to 100 mg/kg in combination with the NSAID fenbufen.

Quinolone antibacterials have been shown to cause arthropathy in immature animals. There is no evidence of arthropathy in fully mature rats and dogs given gatifloxacin for 6 months at doses of 240 or 24 mg/kg, respectively (approximately 1.5 times the maximum human dose in both species based on systemic exposure). Arthropathy and chondrodysplasia were observed in immature dogs given 10 mg/kg gatifloxacin orally for 7 days (approximately equal to the maximum human dose based upon systemic exposure) [see **WARNINGS**]. The relevance of these findings to the clinical use of gatifloxacin is unknown.

Some members of the quinolone class have been shown to cause prolongation of the QT interval in dogs. Intravenous 10-mg/kg bolus doses of gatifloxacin had no effect on QT interval in anesthetized dogs.

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grows Aerobically* - Fourth Edition; Approved Standard, NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Sixth Edition; Approved Standard, NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January 1997.